Effect of Pregnancy and Hormonal Changes on Asthma

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Disclosure

Nothing to disclose

Learning Objectives

At the conclusion of this session, the participant should be able to:

- Describe recent studies on the effects of menarche and menopause on asthma
- Describe recent studies on the effects of pregnancy on asthma
- Discuss implications of these recent findings for patients with asthma

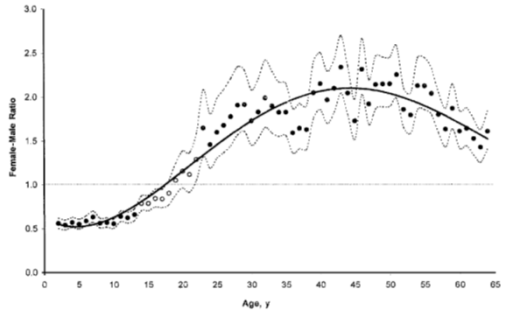
Overview of Presentation

1. Gender/sex-related influences
2. Female sex hormones
3. Menarche → asthma
4. Menopause → asthma
5. Pregnancy → asthma
6. Summary

Gender/Sex-related Influences

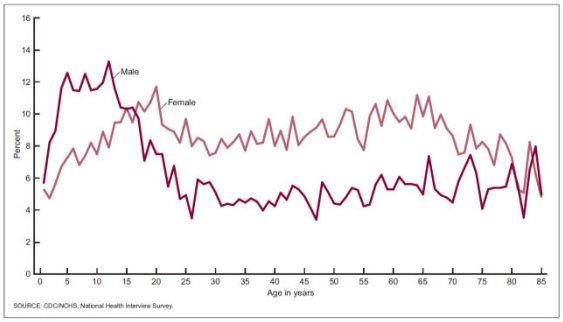
- Complex mixture of influences on asthma:
  - Social and environmental factors (gender-related)
  - Genetic and hormonal factors (sex-related)
- Female vs. male differences in asthma prevalence by age:
  - Children: male >> female
  - Adolescents and adults: female >> male
  - Older adults: female > male

F:M Ratio – Asthma Prevalence by Age



Schatz & Camargo, *Ann Allergy Asthma Immunol* 2003

Prevalence of Current Asthma by Age



Akinbami, *NHSR* 2011

Differences in Asthma-related Events

Compared with men, women have:

- Higher symptom frequency, symptom intensity, and resulting activity limitations
- More ED visits
- More hospitalizations, with longer LOS
- More asthma deaths

Cydulka, *Ann Emerg Med* 2001;
Schatz, *Chest* 2006; many others

Potential Explanations

- Social factors (including diagnostic bias)
- Environmental factors
  - Obesity
  - Sedentary lifestyle
  - Smoking
- Genetics
- Sex hormones

Female Sex Hormones

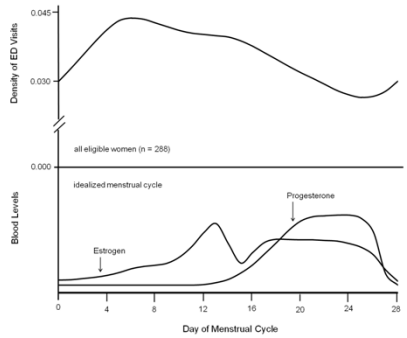
- Estrogen
  - Both immunostimulatory & immunosuppressive
  - Estrogen receptor-α deficient mice have ↑ AHR
  - In humans, unclear association between estrogen levels and AHR or asthma severity/control
- Progesterone
  - Possible relaxation of bronchial smooth muscle
  - In humans, unclear association with progesterone levels and AHR or asthma severity/control

Menarche → Asthma

Traditional highlights:

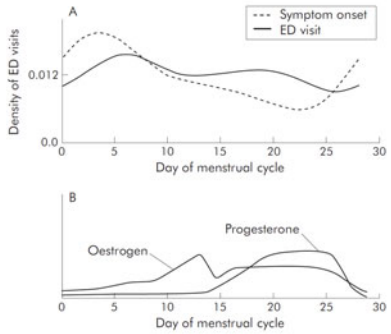
- ↑ risk of incident asthma after menarche
- Premenstrual asthma common
  - 1/3 of asthmatic women
  - Subset with more severe asthma
  - Peak symptoms 2-3 days before menses

ED Visits By Day of Menstrual Cycle



Zimmerman, *AJRCCM* 2000

ED Visits By Day of Menstrual Cycle



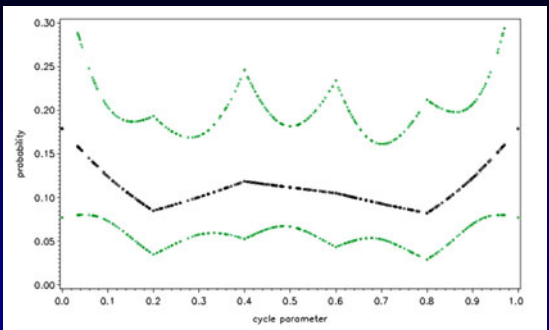
Brenner, *Thorax* 2005

BHR Over Menstrual Cycle

- Swiss cohort study on Air Pollution And Lung Disease in Adults (SAPALDIA)
- 571 menstruating women without hormonal treatment, ages 28-58 years
- Perimenstrual: 3 days before and after first day of menstruation; n=143
- Methacholine challenge; BHR 13%
- Role of oral contraceptive (OC) as effect-modifier; same sample + 130 taking OCs

Dratva, *JACI* 2010

Cyclic Pattern of BHR



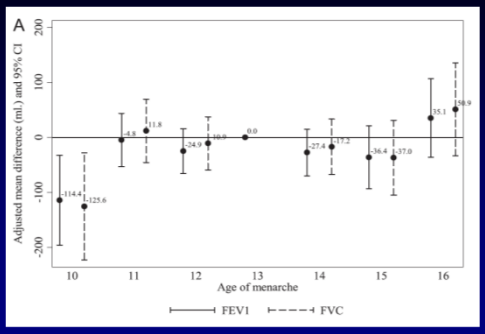
Dratva, *JACI* 2010

Age of Menarche, Lung Function, Asthma

- European Community Respiratory Health Survey II
- 3,354 women, age 27-57 years
- Age of menarche; age ≤10y 3.4%
- Outcomes
  - Spirometry
  - Asthma symptoms
  - Asthma with BHR
  - Asthma symptom score

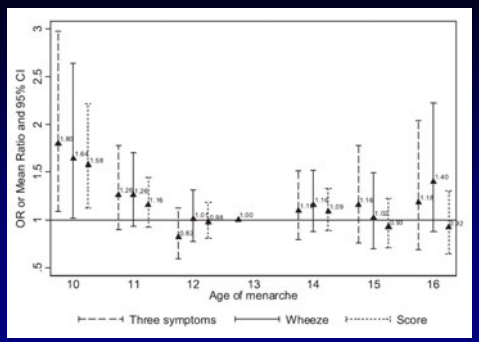
Macsali, *AJRCCM* 2011

FEV_1 and FVC by Age of Menarche



Macsali, *AJRCCM* 2011

Asthma Outcomes by Age of Menarche



Macsali, *AJRCCM* 2011

Age of Menarche and Risk of Asthma

- National Longitudinal Survey of Children & Youth (Canada): age 8-11 y → 18-21 y
- 1,176 girls (weighted n=352,345)
- Early menarche = age <11.56 y (1 SD less then average age of 12.66 y); ~14%
- Report of doctor-diagnosed asthma
- Girls with early menarche had >2x risk of incident asthma during early adulthood (adjusted OR 2.34, 95%CI 1.19-4.59)

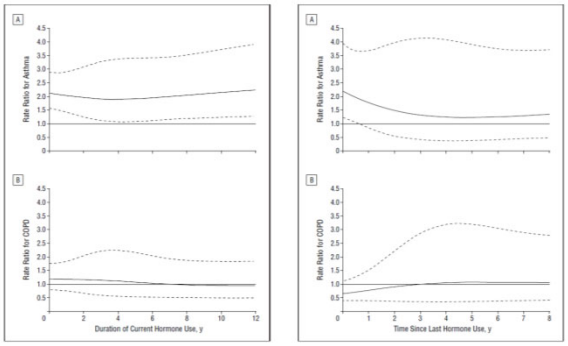
Al-Sahab, *Am J Epidemiol* 2011

Menopause → Asthma

Traditional highlights

- ↓ asthma prevalence in older women lowers the F:M ratio
- Hormone replacement therapy (HRT) ↑ risk of incident asthma
- Menopausal asthma
  - Subset with more severe asthma
  - Absence of atopy; no family history of asthma

Incident Asthma or COPD by HRT



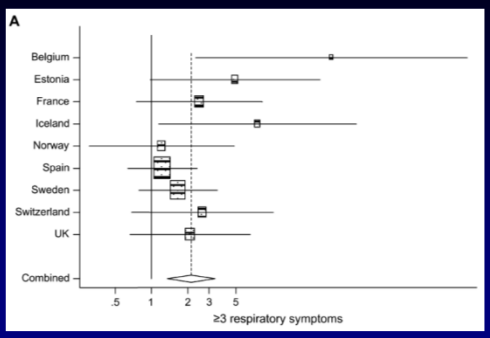
Barr, *Arch Intern Med* 2004

Menopause, Lung Function, Symptoms

- European Community Respiratory Health Survey II, 2002
- 1,274 women, age 45-56 years, not on HRT
- Menopausal transition = amenorrhea for last 6 months (n=432; 34%)
- Outcomes:
  - Spirometry
  - Respiratory symptoms
- Role of BMI as effect-modifier

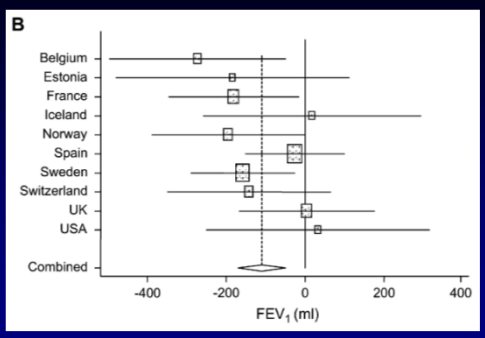
Gomez Real, *JACI* 2008

Amenorrhea and Respiratory Symptoms



Gomez Real, *JACI* 2008

Amenorrhea and FEV_1



Gomez Real, *JACI* 2008

Interaction with BMI ?

	Lower tertile, BMI <23 (n = 344)			Medium tertile, BMI 23-28 (n = 439)		
	Regular menstruations (n = 173)	Amenorrhea (≥6 mo; n = 102)		Regular menstruations (n = 186)	Amenorrhea (≥6 mo; n = 146)	
Lung function	Mean	Mean	Adjusted difference‡ (95% CI)	Mean	Mean	Adjusted difference‡ (95% CI)
FEV_1 (mL)	3006	2690	−166 (−263 to −70)	2860	2672	−54 (−151 to 43)
FVC (mL)	3766	3456	−128 (−241 to −14)	3634	3416	−81 (−191 to 29)
Symptoms	**Percentage**	**Percentage**	**OR‡ (95% CI)**	**Percentage**	**Percentage**	**OR‡ (95% CI)**
Current asthma§	9.7	14	3.07 (1.23-7.7)	11	10	0.66 (0.29-1.50)
≥3 Respiratory symptoms‖	12	27	4.07 (1.88-8.8)	23	28	1.10 (0.61-1.97)
≥3 Respiratory symptoms‖ and allergy¶	8.9	16	3.70 (1.14-12.0)	9.5	13	1.25 (0.42-3.73)
≥3 Respiratory symptoms‖ and no allergy¶	7.4	26	5.71 (1.94-16.70)	25	25	0.82 (0.39-1.73)
Chronic cough and phlegm	3.7	5.3	1.51 (0.35-6.60)	5.4	4.6	0.95 (0.30-3.01)
COPD#	6.8	17.3	2.78 (1.16-6.70)	7.5	9.5	1.08 (0.46-2.55)

Gomez Real, *JACI* 2008

Menopausal Asthma: New Phenotype?

- Three groups of Italian women:
  - 40 with menopausal asthma
  - 35 with premenopausal asthma
  - 30 age-matched healthy controls
- Outcomes:
  - Urinary LTE_4
  - Induced sputum inflammatory cells
  - Exhaled LTE_4, IL-6, pH, NO
- Menopausal: ↑ sputum neutrophils, ↑ exhaled IL-6
- Premenopausal: ↑ sputum eosinophils

Foschino Barbaro, *Allergy* 2010

Pregnancy → Asthma

Traditional highlights:
- Multiple physiologic changes beyond hormones
- Asthma improves for 1/3, same for 1/3, worse for 1/3*
- Mechanism(s) unclear
- Later pregnancies tend to have similar asthma course

NAEPP Working Group Reports:
- 1993
- Update 2004
  http://www.nhlbi.nih.gov/health/prof/lung/asthma/astpreg/astpreg_qr.pdf
- Optimal care improves maternal & fetal outcomes

* Kircher, *Ann Allergy Asthma Immunol* 2002

Pregnancy → Asthma (continued)

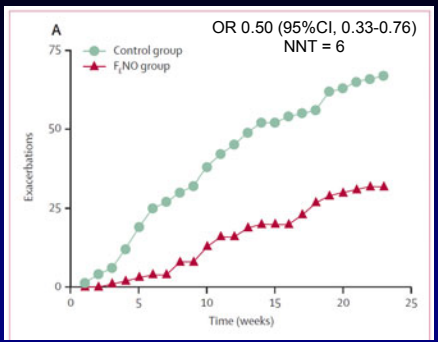
- Effect of pregnancy on asthma
  - No major advances in past 2-3 years
  - eg, relevance of 1/3 rule today is unclear
  - eg, mechanisms for 1/3 rule remain unclear
- Effect of asthma on pregnancy (and children)
  - Multiple recent studies support importance of asthma control for both pregnant mother and child
  - Likewise, multiple studies support overall safety of EPR3 recommendations for pregnant women (benefit >> risk)
- Improve asthma control during pregnancy

F_ENO Measurement During Pregnancy

- Double-blind, parallel-group RCT
- 220 pregnant, non-smoking, Australian women
- Randomly assigned by 22 weeks gestation to ICS adjustment at monthly visits by algorithm:
  - clinical symptoms (control), *versus*
  - F_ENO concentrations (intervention), with uptitration (>29 ppb) or downtitration (<16 ppb) of ICS dose
- Primary outcome: total asthma exacerbations
- ANZCTR 12607000561482

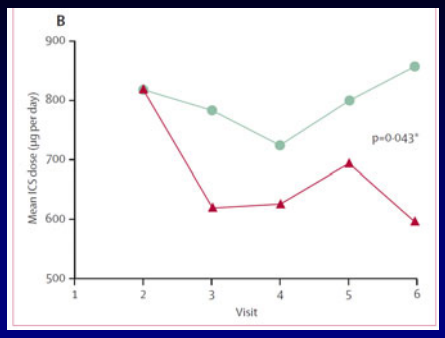
Powell, *Lancet* 2011

F_ENO-guided Care & Asthma Exacerbations



Powell, *Lancet* 2011

F_ENO-guided Care & Maintenance ICS Dose



Powell, *Lancet* 2011

Summary

- Menarche:
  - ↑ BHR during perimenstrual & periovulatory phases
  - Early menarche associated with ↑ adult-onset asthma
- Menopause:
  - In at least some women, menopausal transition associated with ↑ adult-onset asthma
  - Menopausal asthma has ↑ sputum neutrophils
- Pregnancy:
  - Effect of pregnancy on asthma merits investigation
  - F_ENO-guided care may help achieve asthma control